DATA EVALUATION RECORD

IMIPROTHRIN

STUDY TYPE: REPRODUCTION AND FERTILITY EFFECTS STUDY –RAT
OCSPP 870.3800 [§83-4]; OECD 416

MRID 49192901

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects Study – Rat OCSPP 870.3800 [§83-4]; OECD 416.

PC CODE: 004006 **DP BARCODE:** D414392

TEST MATERIAL (PURITY): S-41311 (Imiprothrin; 100% a.i.)

SYNONYMS: (2, 5-dioxo-3-(2-propynyl)-1-imidazolidinyl) methyl (1RS)-cis-trans-chrysanthemate

CITATION: A.M. Hoberman. (1994). Reproductive Effects of S-41311 Administered Orally Via the Diet to Crl:CD®BR VAF/Plus® Rats for Two Generations. Argus research Laboratories, Inc. (Horsham, PA). Laboratory report number 1119-024, December 28, 1994. MRID 49192901. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd. (Chuo-ku, Osaka, Japan)

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 49192901), S-41311 (Imiprothrin, 100% a.i, lot # Y-011001) was administered to groups of 30 F_0 and F_1 Crl:CD®BR VAF/Plus® (Sprague-Dawley) rats/sex/dose in the diet at dose levels of 0, 200, 2000, or 6000 ppm. Pre-mating doses were, respectively: 0, 12.4, 125.5, and 369.4 mg/kg bw/day for F_0 males; 0, 14.7, 143.5, and 423.0 mg/kg bw/day for F_0 females; 0, 15.6, 157.7, and 499.5 mg/kg bw/day for F_1 males; and 0, 17.5, 175.1, and 545.2 mg/kg bw/day for F_1 females. Dosing was as follows: F_0 generation was from 55-56 days of age for 80 days prior to mating, through a maximum of 21 days of mating, and through the gestation and lactation periods (total of 147-148 days for males and 152-154 days for females); F_1 generation was from 21 days of age for up to 84 days prior to mating, through mating, and though gestation and lactation (total of 95-114 days for males and 104-128 days for females). The male rats were terminated after mating, whereas the females were maintained on their respective diets during gestation and lactation. The females were terminated after weaning their litters. Each parental generation produced one litter. Parental systemic toxicity, reproductive function and performance, and offspring viability and growth were evaluated in this study.

F_0 parental rats: There were no treatment-related deaths or clinical signs of toxicity observed in the F_0 parental rats. Body weight gains (m: -17.7%; f: -9.7%) and food consumption values (m: -9.1%; f:-5.2%) were significantly reduced in the 6000 ppm group F_0 male and female rats during the pre-mating period. Mean body weights were significantly reduced in 6000 ppm group males (-5.9 to -11.2%) from pre-mating through termination. Throughout the gestation and lactation

periods, maternal body weights were comparable for all F_0 group dams. F_0 males and females of the 6000 ppm group had significantly reduced terminal body weights (m: -12.5%; f: -5.7%) and significantly increased absolute liver weights (m: 10.8%; f: 11.7%), with resulting significant increases in the liver to body weight ratios (m: 25.2%; f: 18.8%). Histopathologic evaluation of tissues from F_0 male and female rats revealed an increased severity of hemosiderosis in the spleen of the 6000 ppm group males and females and the 2000 ppm group females. No histopathology effects were observed in the livers.

F_1 parental rats: There were no treatment-related deaths or clinical signs of toxicity observed in the F_1 parental rats. During the pre-mating period, body weight gains were significantly reduced in F_1 males and females of the 6000 ppm group (m: -12.8%; f: -10.3%). Mean body weights were significantly reduced in the 2000 ppm group males early in the pre-mating period and in females during most of the pre-mating period (m: -4.2 to -8.5%; f: -4 to -6.1%), and in the 6000 ppm group throughout the pre-mating period (m: -14.1 to -28.4%; f: -11.9 to 27.6%). Food consumption was significantly reduced during 2 or 3 weekly intervals in the 2000 ppm group males during the early pre-mating period and in females midway through the pre-mating period (m: -4.4 to -15.5%; f: -6%), and in the 6000 ppm group males and females throughout the pre-mating period (m and f: -12.1%). Throughout the gestation and lactation periods, maternal body weights (G: -12.1 to -13.6%; L: -7.9 to -12.7%) and food consumption values (G: -13.1%; L: -7.9%) were reduced in F_1 dams in the 6000 ppm group. Terminal body weights were significantly reduced in males of the 6000 ppm group (-14.2%) and in females of the 2000 and 6000 ppm groups (-5.2% and -10.7%, respectively). At 6000 ppm, males also had significantly reduced brain weights (-5.5%) and females had significantly reduced ovarian weights (approximately -20%) and significantly increased liver weights were (16.3%), without concomitant effects on histopathology. As with the parental animals, but to a lesser degree, histopathologic evaluation of tissues from F_1 rats revealed an increased severity of hemosiderosis in the spleen of the 6000 ppm group males and females.

The parental systemic LOAEL in rats was 2000 ppm (125.5 and 143.5 mg/kg bw/day in F_0 males and females; and 157.7 and 175.1 mg/kg bw/day in F_1 males and females, respectively), based on reduced body weight and food consumption in males and females of the F_1 generation and an increased severity of hemosiderosis in the spleen of F_0 generation females. The parental systemic NOAEL is 200 ppm (12.4 and 14.7 mg/kg bw/day in F_0 males and females; and 15.6 and 17.5 mg/kg bw/day in F_1 males and females, respectively). At 6000 ppm (369.4 and 423 mg/kg bw/day in F_0 males and females; and 499.5 and 545.2 mg/kg bw/day in F_1 males and females, respectively), F_0 males displayed a decrease in body weight, and there was an increase in the severity of hemosiderosis in the spleen in both sexes.

There were no treatment-related deaths, clinical observations, or effects on delivery parameters (mean number of implantation sites, liveborn pups, pups dying, delivered litter sizes, sex ratios, and Live Birth or Lactation Indices) in the F_1 or F_2 pups at test substance concentrations as high as 6000 ppm. The F_1 and F_2 pups in the 6000 ppm group had significantly decreased mean body weights during the lactation period (F_1: -9 to -21%; F_2: -7 to -21%). Statistically significant differences were observed in pups (and litters) during skeletal examination of F_2 pups (only generation evaluated) from the 2000 and 6000 ppm groups. These included significant increases in the incidence of unilateral or bilateral 14^{th} ribs skeletal variants in the 2000 and 6000 ppm groups [46 (15), 31 (11), 65 (19) and 88 (22) fetuses (litters), in the 0, 200, 2000 and 6000 ppm

groups, respectively], and bifid thoracic centrum in the 6000 ppm group [5 fetuses (5 litters) in this group versus no incidences in any other group] on PND 4. To a lesser degree, significantly increased incidence of unilateral or bilateral 14th ribs in the 6000 ppm group also was noted on PND 21 examination, [27 (12) versus 1 (1) in the 6000 ppm and control groups, respectively]. The average number of ossified ribs and thoracic vertebrae were significantly increased, and the average number of lumbar vertebrae were significantly decreased in both the 2000 and 6000 ppm groups on PND 4 and in the 6000 ppm group on PND 21 examination. Although the average number of ossification sites were statistically significantly different, the percent change was small (±5%) and not considered biologically significant.

The offspring LOAEL in rat pups was 2000 ppm (125.5 and 143.5 mg/kg bw/day in males and females, respectively), based on increased incidence of rib variants (unilateral or bilateral 14th ribs) in F_2 generation pups. The offspring NOAEL is 200 ppm (12.4 and 14.7 mg/kg bw/day in males and females, respectively). At 6000 ppm (369 and 423 mg/kg/day in F_0 males and females), decreased offspring (F_1 and F_2) body weights and an increase in the incidence of unilateral or bilateral 14th ribs in PND 21 F_2 offspring were observed.

There were no treatment related effects on mating performance, fertility, or reproductive organs in the male or female rats of the F_0 or F_1 generation at dietary levels as high as 6000 ppm, with the exception of reduced ovarian weights in the F_1 females.

The reproductive toxicity LOAEL was not identified; the reproductive toxicity NOAEL in rats is 6000 ppm (369 and 423 mg/kg bw/day in F_0 males and females; and 500 and 545 mg/kg bw/day in F_1 males and females, respectively).

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 2-generation reproductive toxicity study [OCSPP 870.3800; OECD 416] in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: S-41311

Description:	Yellowish brown viscous liquid; faint characteristic odor
Lot #:	Y-011001
Purity:	100% a.i.
Compound stability:	Stored at room temperature; information on stability was not provided in the study report.
CAS # of TGAI:	72963-72-5
Structure:	Not available

2. Vehicle and/or positive control: Certified Rodent Chow® #5002 (Purina Mills, Inc.), Batch # B-1119-024.

3. Test animals:

Species:	Rat (male and female)	
Strain:	Charles River Crl:CD®BR VAF/Plus® (Sprague Dawley)	
Age at study initiation:	(F_0) 8 wks; (F_1) 3 wks	
Wt. at study initiation:	(F_0) Males: 226-304 g; Females: 165-228 g (F_1) Males: 36-71 g ; Females: 34-72 g	
Source:	Charles River Laboratories, Inc. (Portage, MI, USA)	
Housing:	Adult rats were housed individually in wire-bottomed stainless-steel cages (17.5 cm x 17.5 cm x 24 cm) suspended above absorbent paper liners except during the mating and post-mating periods. During the mating periods, male and female rats were housed together (1:1), in the male rat's cage. By gestation day (GD) 20, female rats were individually housed in polycarbonate nesting boxes (20 cm x 23 cm x 45 cm). During the 21-day lactation period, each dam and litter was housed in a common nesting box containing Bed-O'Cobbs® bedding. The bedding was changed at least twice weekly. The F_1 generation weanling rats selected for continued observation were individually housed at 21 days of age.	
Diet:	Certified Rodent Chow® #5002 (Purina Mills, Inc.), *ad libitum*	
Water:	Local, reverse-osmosis water, *ad libitum*, from an automatic watering system or water bottles. Chlorine (0.2-0.7ppm) was added as a bacteriostat.	
Environmental conditions:	**Temperature:**	21.1-25.6°C, with some measures outside the target range
	Humidity:	40-70%, with some measures outside the target range
	Air changes:	10/hr (minimum)
	Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	17 days	

B. PROCEDURES AND STUDY DESIGN:

1. In-life dates: August 27, 1993 to April 21, 1994.

2. Mating procedure: After 80 days of treatment *via* access to the test diets, the F_0 generation male and female rats (1:1) within each dose group were assigned to mating on the basis of a computer-generated table of random units for a maximum of 21 days. The day mating was observed was considered gestation day (GD) 0; observed spermatozoa in vaginal smears or copulatory plugs *in situ* were considered evidence of mating. Pregnant (or presumed pregnant) rats were returned to individual housing with a solid bottom and bedding throughout gestation and lactation. Each female rat that did not mate within the first 14 days of the mating period was assigned an alternate male rat, selected from the male rats in the same group that had previously mated. These rats remained in cohabitation for a maximum of 7 additional days and were returned to individual housing thereafter.

The second (F_1) generation rats were fed the same diets as their parents, beginning on postnatal day (PND) 21. After feeding their respective diets for a maximum of 84 days, the F_1 male and female rats were mated within their same dose groups. During the mating period, the procedures for pairing male and female rats and the determination of evidence of mating and GD 0 were identical to those described previously for the F_0 generation rats. In addition, care was taken to avoid sibling matings. The F_1 generation male rats were sacrificed after completion of mating.

2. **Study schedule:** The F_0 parental animals were approximately 55-56 days old when initially given the test diets, which were available for 80 days before mating, through mating (maximum 21 days) and through the gestation and lactation periods until they were sacrificed after weaning their litters (total 147-148 days for males, and 152-154 days for females). Selection of parents for the F_1 generation was made when the pups were 21 days old, and the animals in the study were approximately 15-19 weeks of age at mating. Selected F_1 generation rats were given the appropriate levels of the test diets from PND 21 (day 1 of observation, pre-mating) for a maximum of 84 days before mating, through mating (maximum 21 days), and through gestation and lactation until they were sacrificed after weaning their litters (total 95-114 days for males, and 104-128 days for females). The third generation (F_2) rats remained with the dam until sacrifice on PND 21. It was assumed pups (F_1 and F_2) were exposed to the test diet *in utero* and via maternal milk during lactation.

3. **Animal assignment:** Table 1 summarizes the number animals assigned to each test group. The F_0 generation rats were selected for study on the basis of physical appearance and body weight. A computer-generated (weight-ordered) randomization procedure was performed to assign these rats to the control, low, mid-, and high- dose test groups as seen in Table 1.

   The F_1 generation litters remained with the F_0 dams until PND 21. A table of random units was used to identify one F_1 generation pup/sex/litter for continued observation. Additional pups were chosen from randomly selected litters as necessary to obtain a total of 30 pups/sex/group, to continue the study as parents for the F_2 generation.

TABLE 1. Animal assignment

Test group	Concentration in diet [a] (ppm)	Animals/group			
		F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low (LDT)	200	30	30	30	30
Mid (MDT)	2000	30	30	30	30
High (HDT)	6000	30	30	30	30

[a] Data obtained from pages 48 and 50 of the study report (MRID 49192901).

4. **Dose selection rationale:** The dose levels were selected based on the results from a range-finding study (Argus, Protocol 1119-024P) where oral administration up to 10,000 ppm of S-41311 in the diet resulted in reductions in body weight, body weight gain, and food consumption values in parental animals and reduced body weights in pups in the 6000 and 10,000 ppm groups. However, the magnitude of the body weight deficits was not provided. See Appendix 1 for further details.

5. **Dosage preparation and analysis:** Formulations were prepared at least weekly by mixing appropriate amounts of test substance (warmed to approximately 70ºC in a hot water bath) with the meal form of Certified Rodent Chow® #5002 using a Hobart mixing bowl for 15 minutes, followed by mixing in a Twin Shell blender for a total of 30 minutes. Formulations were stored in sealed plastic containers at room temperature for up to 7 days of use. Prior to the start of the study, stability of the test substance in rodent chow was evaluated for a period of 14 days at room temperature. Homogeneity (samples taken from the top, middle, and bottom) was evaluated once prior to the start of the study using multi-dimensional high performance liquid chromatography (HPLC). Verification of the concentration of the test substance in feed was performed the week the first test diets were provided and at least monthly thereafter.

Results:

Homogeneity analysis: Mean measured concentrations of the 200, 2000, and 6000 ppm treated diets were 190 ppm (range: 181-199 ppm), 1870 ppm (range: 1840-1940 ppm), and 5520 ppm (range: 5230-6030 ppm), respectively. The relative standard deviation (RSD) for the test diets was 5% or less. Test substance was not detected in the vehicle control formulation.

Stability analysis: Mean concentrations of dosing formulations following 14 days at room temperature were 165 ppm (86.8% of Day 0 concentration), 1700 ppm (90.9% of Day 0 concentration), and 5320 ppm (96.4% of Day 0 concentration) for the 200, 2000, and 6000 ppm treated diets, respectively. A second stability analysis resulted in mean concentrations of 181 ppm (87.4% of Day 0 concentration), 1770 ppm (91.7% of Day 0 concentration), and 5250 ppm (94.8% of Day 0 concentration). After 14 days, all test diets were within ±13% of the initial concentration.

Concentration analysis: The mean concentrations of the 200, 2000, and 6000 ppm treated diets ranged from 178-214 ppm (89-107% of target), 1750-2000 ppm (87.5-100% of target), and 5320-5820 (88.7-97.7% of target), respectively. All concentration results for test diets fed to the rats were within ±13% of the target values.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable. Stability of the test substance for up to 14 days was established before the start of the study for all concentrations.

C. OBSERVATIONS:

1. **Parental animals:** Observations and the schedule for those observations are summarized in Table 2 and as follows. All rats were observed for viability at least twice each day of the study. During acclimation, all F_0 and F_1 generation rats were examined weekly for clinical observations and general health, and body weights, and daily during the treatment period. Body weights and food consumption values of the F_0 generation rats were recorded weekly throughout the study and on the day of scheduled sacrifice (male rats) or until mating (female rats). Additionally, body weights and food consumption values were recorded for the female rats during the gestation and lactation periods as outlined in Table 2. Because pups begin to

consume maternal food on approximately LD 14, food consumption values for the F_0 female rats were not tabulated after LD 14. F_0 generation female rats that did not deliver a litter by day 25 of presumed gestation were continued on study for another 26 to 48 days until sacrifice.

Maternal behavior of the F_0 and F_1 generation dams that naturally delivered litters was recorded when the pups were weighed during the 21-day lactation period. Deviations from expected maternal behavior also were recorded, when and if observed, on all other days of the lactation period.

Vaginal cytology of the F_0 and F_1 generation female rats was evaluated throughout the mating period (a maximum of 21 days) to determine estrous cycle and mating status until presumed GD 0 was identified. The F_0 and F_1 generation female rats were evaluated for duration of gestation (day 0 of presumed gestation to the day the first pup was observed) and length of parturition.

TABLE 2. Parental (F_0 and F_1) Observations [a]

Observation	Time of observation			
	Daily	Weekly	Gestation Period	Lactation Period
Males				
Viability	2x			
Clinical observations	X			
Body Weight		X		
Food Consumption		X		
Females				
Viability	2x			
Clinical observations	X			
Body Weights		X [b]	GD 0, 6, 10, 15, 20, 25 [c]	LD 1, 4, 7, 10, 14 [d], 16, 18, 21 and at sacrifice
Food Consumption		X [b]	Daily	Daily
Stage of estrous	X [e]			

[a] Data obtained from pages 36-41 and 542-548 in the study report (MRID 49192901).

[b] During acclimation (or pre-mating for F_1 generation) and mating period.

[c] If required on GD 25.

[d] After LD 14, it is expected that pups will begin to consume maternal food.

[e] During mating period, until mating is confirmed.

3. <u>Litter observations</u>: Litter observations (X) are summarized in Table 3. The F_0 and F_1 generation female rats were evaluated for delivered litter size, and pup viability during the 21 day postpartum period. Pups that either appeared stillborn or that died before initial viability examination were examined for vital status at birth as follows: lungs were removed from pups and placed in water; if the lungs sank, the pup was considered stillborn, if the lungs floated, the pup was considered liveborn and died shortly after birth. Physical observations (including gross external physical anomalies) were recorded daily for the pups during the postpartum period. Pup body weights, sex and maternal/litter interactions were recorded on PNDs 1 (birth), 4, 7, 14 and 21. On PND 4, litters were standardized to a maximum of 8 pups/litter (4/sex/litter, as nearly as possible); excess pups were killed and discarded. The F_1 generation pups randomly selected for continuation on study were weaned on PND 21. F_2 pups were examined for skeletal alterations on PNDs 4 and 21. Dead pups were examined

grossly for external and internal abnormalities, and a possible cause of death was determined for pups born or found dead. Landmarks of sexual maturation (e.g., anogenital distance; onset of sexual maturation) were not measured.

TABLE 3. Offspring (F_1 and F_2) Litter Observations [a]

Observation	Time of observation (postnatal day)						
	Daily [b]	PND 1	PND 4 [c]	PND 4 [d]	PND 7	PND 14	PND 21
Litter size	X	X	X	X	X	X	X
Sex of each pup (M/F)		X					
Body weight		X	X	X	X	X	X
Viability	2x						
Clinical observations	X						
External malformations	X						
Skeletal alterations (F_2 only)			X				X

[a] Data obtained from pages 36-41 and 542-548 in the study report (MRID 49192901).

[b] From birth through weaning (PND 1-21).

[c] Before standardization (culling)

[d] After standardization (culling)

3. Postmortem observations:

a. Parental animals: F_0 and F_1 generation male rats were sacrificed on days 147 or 148 of the study or between days 95 and 114 of study, respectively. F_0 generation female rats were sacrificed after weaning of the F_1 generation litters, between days 33 to 52 postpartum (total 152-154 study days). F_1 generation female rats were sacrificed on day 21 postpartum (total 104-128 study days). Females that did not deliver a litter were sacrificed up to 48 days after 25 days of presumed gestation. Sacrificed animals were subjected to postmortem examinations as follows:

Complete necropsies were performed on all F_0 and F_1 generation rats after sacrifice by carbon dioxide asphyxiation. Necropsy included an initial examination of external surfaces and all orifices, as well as an internal examination of tissues and organs *in situ*. External and internal portions of all hollow organs; external surfaces of the brain and spinal cord; nasal cavity and neck with associated organs and tissues; thoracic, abdominal and pelvic cavities with associated organs and tissues; and musculo/skeletal carcasses were examined. The liver, spleen, brain and pituitary gland from all F_0 and F_1 generation rats were excised and weighed. Male reproductive organs (each testis and epididymis, the seminal vesicles with associated coagulating gland, and the prostate) and female reproductive organs (the uterus and cervix and each ovary) were excised and weighed. The uteri of F_0 and F_1 generation rats that did not deliver by day 25 of presumed gestation were stained with 10% ammonium sulfide to confirm the presence or absence of implantation sites. Rats that were found dead or sacrificed moribund were necropsied on the day the event occurred as described for scheduled sacrifice.

Tissues from the F_0 and F_1 generation rats marked with an "X" were preserved in neutral buffered 10% formalin for possible histopathological evaluation. The retained organs and tissues of each F_0 and F_1 generation rat in the control and high test diet concentration groups were stained with hematoxylin and eosin and analyzed for microscopic findings

after paraffin embedding and sectioning at approximately 6 microns. If lesions attributable to the test substance were observed in rats in the high concentration group, the same organs were examined microscopically in rats in the lower concentration group. All tissues examined from one randomly selected control male rat and one randomly selected control female rat were retained in order to provide control tissues for any possible comparative histopathological evaluation of gross lesions.

The following tissues (X) were prepared for microscopic examination and weighed (XX):

	Females		**Males**
XX	Ovaries	XX	Testes
XX	Uterus	XX	Epididymides
XX	Vagina/cervix	XX	Prostate
X	Mammary gland	XX	Seminal vesicles with coagulating gland
X	Lesions	X	Lesions
XX	Liver	XX	Liver
XX	Spleen	XX	Spleen
XX	Brain	XX	Brain
XX	Pituitary gland	XX	Pituitary gland

b. Offspring: Pups were culled on PND 4 by carbon dioxide asphyxiation, necropsied and examined for gross lesions. Culled F_1 generation pups with gross lesions and pups found dead on PNDs 1-4 with gross lesions were preserved in Bouin's solution. The F_1 offspring not selected as parental animals and all F_2 offspring were sacrificed at PND 21. All F_2 generation pups were retained in alcohol and examined for skeletal alterations after staining with alizarin red S. Tissues with gross lesions were preserved in neutral buffered 10% formalin. Necropsy of all pups included an examination of the brain for hydrocephaly (a cross-section was made at the suture of the frontal and parietal bones).

D. DATA ANALYSIS:

1. Statistical analyses: Paternal, maternal and pup incidence data were analyzed using the Variance Test for Homogeneity of the Binomial Distribution. The litter was the unit of analysis for the gross litter observation data. Individual pups and litters were the unit of analysis for the necropsy observation data. Adult body weights, body weight changes, food consumption values, organ weights, organ weight/body weight ratios and organ weight/brain weight ratios and litter averages for pup body weights, percent male pups, percent mortality and cumulative survival were analyzed using Bartlett's Test of Homogeneity of Variances and the Analysis of Variance (ANOVA), when appropriate (i.e., if Bartlett's Test was not significant, $p>0.05$). If the ANOVA was significant ($p\leq0.05$), Dunnett's Test was used to identify the statistical significance of the individual groups. If the ANOVA was not appropriate (i.e., if Bartlett's Test was significant, $p\leq0.05$), the Kruskal-Wallis Test was used; when 75% or fewer ties were present; Fisher's Exact Test was used. In cases where the Kruskal-Wallis Test was statistically significant ($p\leq0.05$), Dunn's Method of Multiple Comparisons was used to identify the statistical significance of the individual groups. All other natural delivery data were evaluated by the Kruskal-Wallis Test, when 75% or fewer ties were present. In cases where statistical significance occurred ($p\leq0.05$), Dunn's Method

of Multiple Comparisons was used to identify the statistical significance of the individual groups.

2. Indices:

Reproductive indices: The following reproductive indices were calculated from breeding and parturition records of animals in the study:

$$\text{Mating Index} = \frac{\text{Number of rats that mated}}{\text{Number of rats paired}} \times 100\%$$

$$\text{Fertility Index} = \frac{\text{Number of pregnancies}}{\text{Number of rats that mated}} \times 100\%$$

$$\text{Gestation Index} = \frac{\text{Number of dams with live litters}}{\text{Number of pregnant rats}} \times 100\%$$

Offspring viability indices: The following viability indices were calculated from lactation records of litters in the study:

$$\text{Post-implantation losses (Calculated by Reviewer)} = \frac{\text{Number of implantations} - \text{Number of viable fetuses}}{\text{Number of implantations}} \times 100\%$$

$$\text{Live Birth Index} = \frac{\text{Number of pups born alive}}{\text{Number of pups born}} \times 100\%$$

$$\text{Viability Index} = \frac{\text{Number of live pups on PND 4 (pre-culling)}}{\text{Number of liveborn pups on PND 1}} \times 100\%$$

$$\text{Lactation Index} = \frac{\text{Number of live pups on PND 21}}{\text{Number of live pups on PND 4 (post-culling)}} \times 100\%$$

3. Historical control data: Historical control data were compiled from pregnant control group CD rats in studies conducted from January 1990 to June 1992. Data included reproductive parameters (e.g., numbers of corpora lutea, implantations, resorptions, litter size, sex ratio, fetal body weight) from 2565 pregnant females in 147 studies; fetal external alterations from 2152 litters in 123 studies; fetal soft tissue alterations from 1110 litters in 51 studies; fetal skeletal alterations from 1092 litters in 50 studies; and fetal ossification sites from 993 litters in 46 studies.

II. RESULTS:

A. PARENTAL ANIMALS:

1. Mortality and clinical signs: There were no treatment-related deaths or clinical observations in the F_0 or F_1 parental rats. All clinical observations were considered unrelated

to exposure to S-41311 at concentrations as high as 6000 ppm because: 1) the incidences were not dose-dependent; 2) the observations occurred in only one rat or a few rats within a group; or 3) the observation was associated with other events unrelated to the test substance. Clinical observations were common observations and unrelated to treatment, including: dental problems (missing, broken or misaligned incisors), chromodacryorrhea, chromorrhinorrhea, localized alopecia, and various body lesions.

Two F_0 male rats died prior to scheduled sacrifice: one 200 ppm group rat (10738) was found dead and one 2000 ppm group rat (10764) was sacrificed moribund, each on study day 113. The rat in the 2000 ppm group had limited use of its hindlimbs on study days 112 and 113, believed to have resulted from a systemic lymphosarcoma. The condition was not related to treatment as it was a single event, and this finding occurs spontaneously in this strain of rat.

In the F_1 generation, two male rats were found dead during the pre-mating period: one from the control group (14816) on day 107 and one from the 2000 ppm group (14886) on day 12. The control group rat had lesions (neck and back) and localized alopecia (neck and limbs) during the pre-mating period. The cause of death was presumed related to the dilatation of the renal pelvis, a common spontaneous lesion in this strain of rat. The 2000 ppm group rat death was considered accidental (cage injury).

2. **Body weight and food consumption:** Selected body weight, body weight gain, and food consumption results are summarized in Tables 4a. 4b, 4c and 4d as follows:

a. Pre-mating:

1. F_0 generation:

Males: Body weight gains were significantly reduced in the 6000 ppm group F_0 male rats during several weekly intervals between days 54 to 138, for the pre-mating period (days 1 to 80, -17.7%), and the entire study period (days 1 to 145 ,-20.8%). During the post-mating period (days 103 to 145), average body weight gains were significantly reduced -20% and -30% for the 2000 and 6000 ppm group rats, respectively. Mean body weights were significantly reduced in this group from study day 5 to day 145 (-5.9 to -11.2%). At day 145, the average body weights were 96%, 96% and 87% of the control group value for the 200, 2000 and 6000 ppm groups, respectively. The reductions in the 6000 ppm group increased in magnitude with time and were considered related to the test substance. However, those differences in the 2000 ppm group were not considered adverse since the difference was small (-4%) and no significant differences in average body weights occurred over the entire study period. Other significant reductions during individual intervals in individual dose groups were not considered related to the test substance since they were not dose-dependent and did not occur consistently over time (Table 4a).

Absolute food consumption (g/animal/day) was significantly reduced in the 2000 and 6000 ppm groups on study days 1 to 5, associated with taste aversion. Food consumption values in the 6000 ppm group were significantly reduced for most weekly intervals from days 26 to 138, and overall for the pre-mating period (days 1 to 80, -9.1%), post-mating (103 to 145), and during the entire treatment period (1 to 145, -8.7%). Average body weight gains, body weights, and food consumption values for

the 200 and 2000 ppm groups were comparable to the control group values.

Females: The 6000 ppm group F_0 females had significantly decreased body weight gains on study days 1 to 5 and for the entire pre-mating period (days 1 to 80, -9.7%), and significantly decreased body weight on day 5 (-6.6%). This was related to the significant reduction in absolute food consumption (g/day) during the pre-mating period on days 1 to 5 (-36.8%), for most weekly intervals between days 47 to 80 (-6.1%/-10.4%), and overall from 1 to 80 (-5.2%) in the 6000 ppm group rats. The initial reduction in food consumption on days 1 to 5, was associated with taste aversion and was followed by an increase in consumption. The effect in the 6000 ppm group was considered related to the test substance as it persisted for the entire pre-mating period. Average body weights, body weight gains and food consumption for the 200 and 2000 ppm groups were comparable to the control group values for the entire pre-mating period; isolated significant differences in the 2000 ppm group were not considered treatment related (Table 4a).

2. F_1 generation:

Males: Body weight gains were significantly reduced in F_1 males of 6000 ppm group during practically all weekly intervals from pre-mating days 1 to 78, and overall from days 1 to 78 (-12.8%), and 1 to mating (day 86 or up to 105, -11.4%). Body weights were significantly reduced in the 2000 ppm group on days 1 through 36 (-4.2 to -8.5%) and in the 6000 ppm group on all days (-14.1 to -28.4%). Food consumption (g/day) was significantly reduced in the 2000 ppm group during weekly intervals from pre-mating days 1 to 29 (except days 15-22) and in the 6000 ppm group during all intervals (-12.1%, except days 43 to 50). Exposure to concentrations of the test substance up to 200 ppm did not affect body weight gain, body weight, or food consumption values (Table 4b).

Females: Body weight gains were significantly reduced in F_1 females of the 6000 ppm group on pre-mating days 1 to 15, 29 to 36, and overall on days 1 to 78 (-10.3%). Average body weights were significantly reduced in the 6000 ppm group throughout the pre-mating period (-11.9 to 27.6%) and in the 2000 ppm group on recorded days 8 to 22 and 50 to 78 (-4 to -6.1%). Absolute food consumption values (g/day) were significantly reduced in the 6000 ppm group at all weekly intervals during the pre-mating period (except days 22 to 29) and overall from days 1 to 78 (-12.1%), and in the 2000 ppm group on days 43 to 57 (6%). These events were considered effects of the test substance because they occurred in the two highest dose groups. Exposure to concentrations of the test substance up to 200 ppm did not affect average body weights, body weight gains, or food consumption values during the pre-mating period (Table 4b).

b. Gestation and lactation:

1. F_0 generation: Maternal body weight gains, body weights, and food consumption values were comparable throughout the gestation and lactation periods for all F_0 group dams, with few exceptions (Table 4c). During lactation, body weight gains were significantly increased for LDs 1 to 21 in the 2000 and 6000 ppm groups and

body weights were significantly decreased for LDs 1 and 4 in the 6000 ppm group. These differences were attributed to normal changes in body weight gains and body weights during lactation and not to the test substance, as the average body weight change in this group was greater than in the control group.

2. **F_1 generation:** Significantly reduced body weights persisted in the F_1 dams in the 6000 ppm group during the gestation (-12.1 to -13.6%) and lactation (-7.9 to -12.7%) periods (Table 4d), with significantly reduced body weight gains on GDs 0 to 6 (body weight gains tended to be lower overall, but the difference was not significant). Absolute food consumption values were significantly reduced in the 6000 ppm group for all weekly intervals during gestation and overall from GD 0 to 20 (-13.1%), and on LDs 7 to 10, 10 to 14, and overall from LD 1 to 14 (-7.9%). These reductions were considered related to the test substance. The 6000 ppm group had significantly increased body weight gain on LDs 1 to 21. Maternal body weights, body weight gains, and food consumption values were unaffected by the 200 and 2000 ppm concentrations of the test substance during the gestation and lactation periods.

TABLE 4a. Selected mean (±SD) body weight and food consumption - pre-mating: F_0 generation [a]

Observations/study days	Dietary concentration (ppm)			
	Control	200	2000	6000
F_0 Generation males- Pre-mating				
Number of animals	30 [b]	30 [b]	30 [b]	30 [b]
Mean body weight (g):				
Day 1	270.5±14.3	269.6±15.5	269.5±13.1	269.4±13.9
Day 19	384.4±24.2	383.1±30.6	382.4±24.4	361.7±26.1** (-5.9)[c]
Day 40	476.3±37.0	467.7±41.8	467.1±31.4	444.1±32.8** (-6.8)
Day 61	543.8±45.0	534.1±48.6	530.9±39.1	494.5±39.1** (-9.1)
Day 80	595.2±50.9	578.6±52.7	575.4±42.8	536.6±42.0** (-9.8)
Day 103 (post-mating)	615.4±52.8	597.4±54.1	597.7±45.0	548.3±42.4** (-10.9)
Day 145	677.2±59.2	650.0±57.6	649.2±51.6	591.4±64.3** (-12.7)
Mean weight gain (g): [d]				
Days 1-19	113.9	113.5	112.9	92.3 (-19)
Days 19-40	91.9	84.6	84.7	82.4 (-10.3)
Days 40-61	67.5	66.4	63.8	50.4 (-25.3)
Days 61-80	51.4	44.5	44.5	42.1 (-18.1)
Days 1-80	324.6±45.2	309.0±43.9	305.9±37.0	267.2±33.1** (-17.7)
Days 103-145 (post-mating)	61.8±13.7	53.8±14.2	49.6±15.5* (-19.7)	43.1±47.2* (-30.3)
Days 1-145	406.7±53.4	380.6±49.4	379.7±44.8	322.0±59.4** (-20.8)
Mean food consumption (g/animal/day):				
Days 1-5	27.0±2.2	27.8±5.0	25.3±2.0** (-6.3)	15.3±3.7** (-43.3)
Days 26-30	29.3±2.8	28.3±2.8	28.6±2.6	26.7±2.2** (-8.9)
Days 47-54	30.2±2.9	29.2±3.2	29.2±2.2	26.6±2.5** (-11.9)
Days 1-80	28.7±2.4	28.1±2.6	28.2±2.2	26.1±2.0** (-9.1)
Days 103-145 (post-mating)	28.2±2.4	27.2±2.1	27.4±2.1	26.0±2.7** (-7.8)
Days 1-145	28.6±2.3	27.8±2.4	28.0±2.1	26.1±2.1** (-8.7)
F_0 Generation females- Pre-mating				
Number of animals	30 [b]	30 [b]	30 [b]	30 [b]
Mean body weight (g):				
Day 1	194.0±12.4	193.6±12.1	195.5±14.0	193.4±11.2
Day 5	206.4±13.2	205.1±13.6	204.4±14.2	192.7±12.0** (-6.6)
Day 40	275.0±20.1	275.4±22.2	281.2±25.3	269.3±16.4
Day 80	311.5±24.4	312.6±27.4	316.6±32.6	299.5±18.9 (-4)

TABLE 4a. Selected mean (±SD) body weight and food consumption - pre-mating: F_0 generation [a]

Observations/study days	Dietary concentration (ppm)			
	Control	200	2000	6000
Mean weight gain (g): [d]				
Days 1-5	12.4±4.5	11.6±4.9	8.9±5.5* (-28.2)	-0.7±8.0** (-105.6)
Days 1-40	81	81.8	85.7	75.9 (-6.3)
Days 40-80	36.5	37.2	35.4	30.2 (-17.3)
Days 1-80	117.5±18.2	119.1±21.3	121.1±22.8	106.1±14.2* (-9.7)
Mean food consumption (g/animal/day):				
Days 1-5	18.5±1.4	18.7±1.8	18.2±1.8	11.7±3.3** (-36.8)
Days 47-54	19.6±1.5	20.0±2.1	20.2±2.5	18.4±1.5* (-6.1)
Days 75-80	19.2±4.0	18.4±3.0	17.4±2.7	17.2±2.1* (-10.4)
Days 1-80	19.3±1.7	19.5±1.7	19.4±1.7	18.3±1.3* (-5.2)

[a] Data obtained from pages 116-121, 186-187 and 192 in the study report (MRID 49192901).

[b] Excludes values from animals that died or were moribund sacrificed, values that were incorrectly recorded, and those associated with spillage, interrupted water access or an empty feed jar. (N=29-30 in all cases).

[c] Values in parentheses represent percent difference from control, calculated by the Reviewer.

[d] Means for the intervals 1-19, 19-40, 40-61, and 61-80 were calculated by Reviewer from weekly interval means and not subject to statistical analysis.

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

TABLE 4b. Selected mean (±SD) body weight and food consumption- pre-mating: F_1 generation [a]

Observations/study days	Dietary concentration (ppm)			
	Control	200	2000	6000
F_1 Generation males- Pre-mating				
Number of animals	30 [b]	30 [b]	30 [b]	30 [b]
Mean body weight (g):				
Day 1	58.9±6.2	57.5±5.5	53.9±7.5* (-8.5) [c]	42.2±4.2** (-28.4)
Day 22	237.8±16.7	235.6±16.7	226.5±16.2* (-4.8)	188.4±13.0** (-20.8)
Day 43	417.7±29.4	416.9±29.9	404.7±29.6	353.8±26.9** (-15.3)
Day 64	528.5±43.2	523.2±44.2	507.2±43.5	454.2±38.0** (-14.1)
Day 78	578.0±50.6	571.4±56.9	551.9±49.5	496.0±41.9** (-14.2)
Day 86 to 105 (day 1 mating)	577.9±49.4	583.8±57.8	561.4±52.5	502.2±43.8** (-13.1)
Mean weight gain (g): [d]				
Days 1-22	178.9	178.1	172.6	146.2 (-18.3)
Days 22-43	179.9	181.3	178.2	165.4 (-8.1)
Days 43-64	110.8	106.3	102.5	100.4 (-9.4)
Days 64-78	49.5	48.2	44.7	41.8 (-15.6)
Days 1-78	520.0±48.3	514.1±55.8	498.3±46.4	453.6±39.6** (-12.8)
Mean food consumption (g/animal/day):				
Days 1-8	12.9±2.2	12.1±2.0	10.9±2.4** (-15.5)	8.9±1.9** (-31.0)
Days 22-29	29.5±2.1	29.2±2.6	28.2±2.1* (-4.4)	26.5±2.1** (-10.2)
Days 43-50	31.2±3.4	31.0±3.5	30.5±2.6	29.1±2.7
Days 71-78	31.4±2.9	31.3±3.5	31.0±3.2	28.3±2.4** (-9.9)
Days 1-78	28.1±2.2	27.6±2.5	26.9±2.0	24.7±1.7** (-12.1)
F_1 Generation females- Pre-mating				
Number of animals	30 [b]	30 [b]	30 [b]	30 [b]
Mean body weight (g):				
Day 1	56.1±6.2	56.2±6.4	52.7±5.9	40.7±3.8** (-27.5)
Day 22	186.7±14.5	182.4±15.3	179.2±12.6* (-4.0)	155.8±11.6** (-16.6)
Day 43	261.8±21.5	254.2±21.0	252.5±21.2	227.4±17.2** (-13.1)
Day 64	307.4±27.7	296.0±24.3	291.5±26.2* (-5.2)	268.0±22.1** (-12.8)
Day 78	326.7±33.1	318.5±29.8	308.6±32.0* (-5.5)	283.6±22.4** (-13.2)
Day 86 to 105 (day 1 mating)	325.7±30.7	319.6±30.0	311.2±31.0	287.0±23.5** (-11.9)

TABLE 4b. Selected mean (±SD) body weight and food consumption- pre-mating: F_1 generation [a]				
Observations/study days	**Dietary concentration (ppm)**			
	Control	**200**	**2000**	**6000**
Mean weight gain (g): [d]				
Days 1-22 [b]	130.6	126.2	126.5	115.1 (-11.9)
Days 22-43	75.1	71.8	73.0	71.6 (-4.7)
Days 43-64	45.6	41.8	39.0	40.6 (-11.0)
Days 64-78	19.3	22.5	17.1	15.6 (-19.2)
Days 1-78	270.9±31.7	262.8±27.7	256.4±29.8	243.1±21.8** (-10.3)
Mean food consumption (g/animal/day):				
Days 1-8	10.3±2.4	11.2±2.0	10.6±2.1	8.4±1.7** (-18.4)
Days 22-29	21.4±2.1	20.7±2.1	21.0±2.7	20.1±1.3
Days 43-50	21.7±2.5	20.7±1.8	20.4±1.7* (-6.0)	19.2±1.6** (-11.5)
Days 71-78	20.8±2.7	20.4±1.7	19.3±2.4	18.2±1.3** (-12.5)
Days 1-78	19.9±2.0	19.5±1.5	19.0±1.7	17.5±1.0** (-12.1)

[a] Select data obtained from pages 324-327, 383-384 and 389 in the study report (MRID 49192901).

[b] Excludes values from animals that were found dead, values for days that data were not recorded (day 64 or 71 were the last days some of the youngest rats in a group were weighed), and values associated with spillage. F_1 males on day 78: N=25, 26, 25, and 24 in the 0, 200, 2000, and 6000 ppm groups, respectively. F_1 females on day 78: N=26, 26, 27, and 26 in the same respective groups.

[c] Values in parentheses represent percent difference from control, calculated by Reviewer.

[d] Means for the intervals 1-19, 19-40, 40-61, and 61-80 were calculated by Reviewer from weekly interval means and not subject to statistical analysis.

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

TABLE 4c. Selected mean (±SD) body weight and food consumption- gestation and lactation: F_0 generation [a]				
Observations/study days	**Dietary concentration (ppm)**			
	Control	**200**	**2000**	**6000**
F_0 Generation females: Gestation				
Number of animals	25 [b]	23	26 [b]	21 [b]
Mean body weight (g)				
Day 1	314.4±28.1	304.9±23.7	313.2±27.2	301.4±19.4 (-4.1) [d]
Day 20	447.1±42.4	433.4±38.6	443.7±37.0	429.4±25.7
Mean weight gain (g): [c]				
Days 0-20	132.7±23.2	128.5±19.6	130.5±23.8	127.0±20.1
Mean food consumption (g/animal/day):				
Days 0-20	24.4±2.5	24.7±1.7	24.2±2.5	23.7±2.4
F_0 Generation females: Lactation				
Number of animals	25 [b]	23 [b]	26 [b]	21 [b]
Mean body weight (g):				
Day 1	355.4±29.4	347.3±26.0	340.5±26.0	327.7±23.4** (-7.8) [d]
Day 10	372.7±24.8	366.0±24.3	363.9±24.6	357.0±19.3 (-4.2)
Day 21	363.7±27.3	364.0±27.4	368.6±22.2	369.6±12.6
Mean weight gain (g): [c]				
Days 1-10	17.3	18.7	23.4	29.3
Days 10-21	-9.0	-2.0	4.7	12.6
Days 1-21	9.8±19.2	16.7±20.9	29.6±15.7** (2x)	41.9±19.7** (3.3x)
Mean food consumption (g/animal/day):				
Day 1-14	45.3±5.9	43.9±5.6	45.3±4.1	42.3±4.6

[a] Select data obtained from pages 188-191, 194, and 196 in the study report (MRID 49192901).

[b] Excludes values for a control rat with no confirmed mating date, values for a 2000 ppm dam with no surviving pups after PND 1, values associated with interrupted water access or spillage. For body weight data, F_0 females minimum: N=23, 23, 24, and 20 in the 0, 200, 2000, and 6000 ppm groups, respectively. For food consumption data, F_0 females minimum: N=24, 22, 24, and 20 in the same respective groups

[c] Means for the intervals 1-19, 19-40, 40-61, and 61-80 were calculated by Reviewer from weekly interval means and not subject to statistical analysis..

[d] Values in parentheses represent percent difference from control, calculated by Reviewer.

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

TABLE 4d. Selected mean (±SD) body weight and food consumption- gestation and lactation: F_1 generation [a]

Observations/study days	Dietary concentration (ppm)			
	Control	200	2000	6000
F_1 Generation females: Gestation				
Number of animals	23	23	22 [b]	25
Mean weight (g):				
Day 1	326.3±34.1	313.8±29.9	308.8±31.8	283.8±26.1** (-13.0) [c]
Day 6	356.7±31.6	345.6±32.6	341.4±35.4	308.5±37.0** (-13.5)
Day 10	377.3±34.5	363.6±33.5	359.9±35.0	326.0±26.6** (-13.6)
Day 15	400.3±36.5	389.0±35.6	386.9±35.6	351.2±26.8** (-12.3)
Day 20	467.9±38.8	450.4±37.9	446.6±45.1	411.1±30.6** (-12.1)
Mean weight gain (g): [d]				
Days 0-6	30.4±8.6	31.8±9.0	32.6±8.4	24.6±10.2* (-19.1)
Days 6-20 (treatment)	111.2	104.8	105.2	102.6 (-7.7)
Days 0-20	141.6±18.1	136.6±24.9	137.8±22.0	127.3±19.0 (-10.1)
Mean food consumption (g/animal/day):				
Days 0-6	23.9±2.9	23.8±3.1	23.0±3.4	19.8±2.5** (-17.2)
Days 6-10	26.3±3.6	25.4±3.6	25.3±3.9	22.2±2.8** (-15.6)
Days 0-20	25.1±2.5	24.6±2.8	24.3±2.9	21.8±2.0** (-13.1)
F_1 Generation females: Lactation				
Number of animals	23	22 [e]	22	25 [b]
Mean weight (g):				
Day 1	370.3±35.0	358.2±36.6	354.8±32.3	323.2±32.2** (-12.7)
Day 7	374.0±31.8	370.7±32.4	361.4±32.4	333.2±28.1** (-10.9)
Day 14	389.0±33.6	387.4±32.8	382.5±30.3	352.1±31.6** (-9.5)
Day 21	382.9±28.5	377.0±27.0	379.3±24.9	352.5±29.5** (-7.9)
Mean weight gain (g): [d]				
Days 1-7	3.7	12.5	6.6	10.0
Days 7-14	15.0	16.7	21.1	18.9
Days 14-21	-6.1	-10.4	-3.2	0.4
Days 1-21	12.6±17.5	18.8±24.6	24.5±21.1	29.3±18.9* (1.3x)
Mean food consumption (g/animal/day):				
Day 1-4	28.2±5.4	31.6±6.9	29.0±7.7	26.5±4.8
Day 10-14	55.7±5.6	55.4±4.6	56.0±3.9	51.1±3.8** (-8.3)
Day 1-14	44.4±3.6	45.1±4.0	44.6±4.1	40.9±3.4** (-7.9)

[a] Select data obtained from pages 385-388, 391 and 393in the study report (MRID 49192901).

[b] Excludes values associated with spillage or interrupted water access.

[c] Values in parentheses represent percent difference from control, calculated by Reviewer.

[d] Means for the intervals 1-19, 19-40, 40-61, and 61-80 were calculated by Reviewer from weekly interval means and not subject to statistical analysis.

[e] Excludes values from one dam that did not deliver a litter

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

3. <u>Test substance intake</u>: Based on food consumption, body weight, and nominal concentrations of test substance, the range of doses expressed as mean mg test substance/kg body weight/day during the 80 day pre-mating period are presented in Table 5a and 5b.

TABLE 5a. Mean test substance intake during pre-mating (mg/kg body weight/day) [a]						
Generation	Male			Female		
	200 ppm	2000 ppm	6000 ppm	200 ppm	2000 ppm	6000 ppm
F_0	12.4±0.5	125.5±8.5	369.4±15.7	14.7±1.0	143.5±6.3	423.0±18.8
F_1	15.6±0.5	157.7±6.4	499.5±25.5	17.5±0.7	175.1±9.3	545.2±26.4

[a] Data obtained from pages 108, 176, 318 and 373 in the study report (MRID 49192901).

TABLE 5b. Mean test substance intake during gestation and lactation (mg/kg body weight/day) [a]						
Generation	Gestation			Lactation (LDs 1-14)		
	200 ppm	2000 ppm	6000 ppm	200 ppm	2000 ppm	6000 ppm
F_0	13.7±1.0	131.9±11.2	401.3±35.8	24.7±3.1	257.4±25.3	739.5±85.4
F_1	13.2±1.1	131.9±9.9	389.1±34.4	24.4±2.8	244.2±21.1	733.0±69.7

[a] Data obtained from pages 177-178 and 374-375 in the study report (MRID 49192901).

4. Reproductive function:

a. Estrous cycle length and periodicity: No treatment related effects on estrous cycle length and periodicity were noted during the mating period. In the F_0 generation, four, zero, two, and one female in the 0, 200, 2000, and 6000 ppm groups, respectively, had persistent diestrus. In the F_1 generation, three, one, one, and one female in the same respective groups had persistent diestrus. Most females had evidence of mating within one week of pairing.

b. Sperm measures: Sperm parameters were not evaluated.

5. Reproductive performance: Results for the parental animals are summarized in Tables 6a and 6b. No treatment related effects on reproductive performance or function were noted. Exposure to dietary concentrations of S-41311 as high as 6000 ppm did not affect the mating performance or fertility of the male or female rats of either generation. The averages for the days paired, the numbers of male rats mating and the numbers of male rats siring litters (male Fertility Indices), the numbers of female rats that mated and the numbers of mated female rats that were pregnant (female Fertility Indices) were similar among the four groups and did not significantly differ, with one exception. The numbers of F_1 male rats mating was significantly increased in the 200, 2000 and 6000 ppm groups. These increases were not considered related to the test substance but reflected the few rats that mated in the control group.

TABLE 6a. Reproductive performance- F_0 generation [a]				
Observation	Dietary concentration (ppm)			
	Control	200	2000	6000
F_0 Generation				
Number paired (male/female)	30/30	30/30	30/30	30/30
Number mated (male/female)	29/30	29/30	29/30	29/29
Number fertile (male/female)	25/25	22/23	25/26	21/21
Intercurrent deaths (male/female)	0/0	1/0	1/0	0/0
Mean (±SD) precoital interval (days)	3.9±3.9	3.1±3.0	3.8±3.0	3.4±4.1
Mean (±SD) gestation interval (days)	22.9±0.6	23.0±0.6	23.0±0.4	22.9±0.3
Total implantation sites Mean/dam (±SD)	398 15.9±4.1	343 14.9±4.6	401 15.4±3.8	336 16.0±2.8

TABLE 6a. Reproductive performance- F_0 generation [a]				
Observation	**Dietary concentration (ppm)**			
	Control	**200**	**2000**	**6000**
Post-implantation loss [b] Number of lost implantations Mean % (±SD)	 54 13.6	 59 17.2	 38 9.5	 27 8.0
Number with total litter loss	0	0	0	0
Number with live born litters	25	23	26	21
INDICES				
Mating index (female)	100%	100%	100%	96.7%
Fertility index (male)	86.2%	75.9%	86.2%	72.4%
Fertility index (female)	83.3%	76.7%	86.7%	72.4%
Gestation index (female)	100%	100%	100%	100%

[a] Data obtained from pages 124 and 198-199 in the study report (MRID 49192901).

[b] Calculated by the Reviewer from data on pages 199-200 in the study report, not subject to statistical analysis.

TABLE 6b. Reproductive performance- F_1 generation [a]				
Observation	**Dietary concentration (ppm)**			
	Control	**200**	**2000**	**6000**
F_1 Generation				
Number paired (male/female)	30/30	30/30	29/30	27/30
Number mated (male/female)	24/28	27*/30	28**/30	27**/30
Number fertile (male/female)	20/23	23/23	21/22	23/25
Intercurrent deaths (male/female)	1/0	0/0	1/0	3/0
Mean (±SD) precoital interval (days)	5.8±6.7	4.4±5.4	3.0±2.8	2.9±2.2
Mean (±SD) gestation interval (days)	22.8±0.4	22.9±0.5	22.8±0.4	23.0±0.4
Total implantation sites Mean/dam (±SD)	385 16.7±1.7	353 16.0±3.7	348 15.8±3.0	400 16.0±2.2
Post-implantation loss [b] Number of lost implantations Mean %	 28 7.3	 38 10.8	 33 9.5	 22 5.5
Number with total litter loss	0	0	0	0
Number with live born litters	23	22	22	25
INDICES				
Mating index (female)	93.3%	100%	100%	100%
Fertility index (male)	83.3%	85.2%	75.0%	85.2%
Fertility index (female)	82.1%	76.7%	73.3%	83.3%
Gestation index (female)	100%	95.6%	100%	100%

[a] Data obtained from pages 329 and 395-396 in the study report (MRID 49192901).

[b] Calculated by the Reviewer from data on pages 396-397 in the study report, not subject to statistical analysis.

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

6. Parental postmortem results:

a. Organ weights:

F_0 generation: Selected absolute and relative (to body weight) organ weight values are presented in Table 7a. In the F_0 males and females of the 6000 ppm group, terminal body weights were significantly reduced (m: -12.5% and f: -5.7%) and the absolute liver weights were increased (m: 10.8% and f: 11.7%). Significant increases in the ratios of liver to body weight (m: 25.2% and f: 18.8%) and liver to brain weight (m: 11.3% and f: 12.2%) also were noted in the 6000 ppm group. These events were considered effects of

the test substance. No other effect on organ weights or ratios to body or brain weights were attributed to the test substance. Reflecting the reduced terminal body weights in the 6000 ppm group, the ratios of organ to body weights for the testes, epididymides and brain were significantly increased in males; similarly, ratios of the brain and spleen to body weights were increased in females of this group. The increased ratios of brain to body weight in the 200 ppm group males and of liver to body weight in the 2000 ppm group males and females were not considered treatment related since the absolute weight and the ratio of liver to brain weight (not tabulated) did not significantly differ from the control group values.

F_1 generation: Selected absolute and relative (to body weight) organ weight values are presented in Table 7b. Terminal body weights were significantly reduced in F_1 generation females in the 2000 ppm (-5.2%) and males and females in the 6000 ppm (m: -14.2%; f: -10.7%) groups. In the 6000 ppm group, males had significantly reduced absolute brain weights (-5.5%) and females had significantly reduced ovary weights (approximately -20%) and significantly increased liver weights (16.3%). Reflecting the decreased terminal body weights, the ratios of the testes, epididymides, brain and liver to body weight were significantly increased in the 6000 ppm group males and the ratio of liver to body weight was significantly increased in the 2000 ppm (12.4%) and 6000 ppm (28.3%) group females. The ratios of individual testes and epididymides to brain weight also were significantly increased (~9%) in the 6000 ppm group. In females, the ratios of brain to body weight (9.4%) and liver to brain weight (18.5%) were significantly increased while the ratio of ovary to brain weight (approximately -20%) was significantly decreased in the 6000 ppm group. The changes in liver and ovarian weights were considered related to the test substance. The ratio of brain to body weight was significantly increased in the 200 ppm group while the ratios of spleen to brain weight were significantly decreased in the 200 and 2000 ppm groups. These changes were not considered related to the test substance because: 1) they were not dose-dependent; and 2) no histopathologic changes were observed in the 6000 ppm group tissues. Exposure to concentrations of the test substance as high as 200 ppm (females) or 2000 ppm (males) did not affect absolute weights or the ratio to body or brain weight for any organ evaluated.

Table 7a. Terminal body weight and absolute and relative (to body weight) organ weights- F_0 generation [a]

Observation	Dietary concentration (ppm)			
	0	200	2000	6000
Males				
Number of animals	30	29	29	30
Terminal body weight (g)	694.2±61.4	666.1±59.2	666.2±53.4	607.3±70.9** (-12.5) [b]
Testes (g) (right) Testes (g) (right)	1.94±0.13 [c] 0.28±0.03	1.92±0.14 0.29±0.02	1.90±0.18 0.29±0.03	1.97±0.23 0.33±0.05** (17.9)
Testes (g) (left) Testes (g) (left)	1.93±0.15 0.28±0.03	1.90±0.13 0.28±0.02	1.86±0.28 0.28±0.04	1.98±0.22 0.33±0.05** (17.9)
Epididymides (g) (right) Epididymides (g) (right)	0.78±0.08 0.11±0.02	0.80±0.08 0.12±0.01	0.78±0.08 0.12±0.02	0.78±0.12 0.13±0.02** (18.2)
Epididymides (g) (left) Epididymides (g) (left)	0.77±0.10 0.11±0.02	0.76±0.07 0.11±0.01	0.75±0.08 0.11±0.01	0.77±0.12 0.13±0.02** (18.2)

Table 7a. Terminal body weight and absolute and relative (to body weight) organ weights- F_0 generation [a]				
Observation	**Dietary concentration (ppm)**			
	0	**200**	**2000**	**6000**
Brain (g)	2.19±0.10 0.32±0.03	2.24±0.11 0.34±0.03* (6.3)	2.18±0.09 0.33±0.03	2.18±0.10 0.36±0.06** (12.5)
Liver (g)	24.61±4.17 3.53±0.36	24.25±3.18 3.64±0.31	24.97±3.41 3.73±0.27* (5.7)	27.26±3.55** (10.8) 4.42±0.42** (25.2)
Spleen (g)	0.97±0.14 0.14±0.02	0.99±0.21 0.15±0.03	0.99±0.20 0.15±0.03	0.95±0.20 0.16±0.03
Females				
Number of animals	30	30	30	30
Terminal body weight (g)	350.8±28.8	352.5±32.6	349.9±39.7	330.7±19.6* (-5.7)
Uterus: non-gravid (g)	0.73±0.21 0.21±0.06	0.74±0.13 0.21±0.04	0.73±0.20 0.21±0.06	0.75±0.29 0.23±0.09
Ovary (g) (right)	0.051±0.012 0.015±0.005	0.051±0.012 0.015±0.006	0.053±0.017 0.015±0.005	0.048±0.011 0.015±0.005
Ovary (g) (left)	0.049±0.013 0.014±0.005	0.050±0.014 0.014±0.006	0.053±0.014 0.015±0.005	0.048±0.012 0.015±0.005
Brain (g)	2.00±0.10 0.57±0.05	1.97±0.11 0.56±0.05	2.02±0.10 0.58±0.06	1.99±0.10 0.60±0.05* (5.3)
Liver (g)	13.47±2.10 3.82±0.36	13.71±1.64 3.89±0.37	14.23±1.91 4.06±0.39* (6.3)	15.04±1.59** (11.7) 4.54±0.35** (18.8)
Spleen (g)	0.66±0.13 0.19±0.04	0.64±0.10 0.18±0.03	0.64±0.12 0.18±0.03	0.67±0.07 0.20±0.02* (5.3)

[a] Data obtained from pages 113-114 and 183-184 in the study report (MRID 49192901).

[b] Numbers in parentheses are percent different from the control group, calculated by the Reviewer.

[c] Top row: absolute weight (g), bottom row, relative to body weight (g/kg bw)

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

Table 7b. Terminal body weight and absolute and relative (to body weight) organ weight- F_1 generation [a]				
Observation	**Dietary concentration (ppm)**			
	0	**200**	**2000**	**6000**
Males				
Number of animals	29	30	29	27
Terminal body weight (g)	656.0±60.5	654.7±78.2	626.9±65.6	562.7±56.4** (-14.2) [b]
Testes (g) (right)	1.91±0.16 [c] 0.29±0.03	1.92±0.20 0.30±0.04	1.93±0.17 0.31±0.03	1.98±0.16 0.35±0.04** (20.7)
Testes (g) (left)	1.91±0.15 0.29±0.03	1.93±0.19 0.30±0.04	1.94±0.19 0.31±0.03	1.97±0.16 0.35±0.04** (20.7)
Epididymides (g) (right)	0.75±0.08 0.12±0.02	0.73±0.12 0.11±0.02	0.75±0.08 0.12±0.01	0.77±0.09 0.14±0.02** (16.7)
Epididymides (g) (left)	0.73±0.07 0.11±0.01	0.72±0.10 0.11±0.02	0.73±0.10 0.12±0.02	0.75±0.08 0.13±0.02** (18.2)
Brain (g)	2.20±0.10 0.34±0.03	2.18±0.14 0.34±0.04	2.15±0.12 0.35±0.04	2.08±0.12** (-5.5) 0.37±0.04** (8.8)
Liver (g)	26.34±4.09 4.00±0.40	27.44±5.53 4.17±0.48	26.80±5.11 4.25±0.49	27.27±4.62 4.83±0.54** (20.8)
Spleen (g)	1.05±0.14 0.16±0.02	1.00±0.20 0.15±0.03	0.96±0.16 0.15±0.02	0.94±0.18 0.17±0.03

Table 7b. Terminal body weight and absolute and relative (to body weight) organ weight- F_1 generation [a]				
Observation	**Dietary concentration (ppm)**			
	0	**200**	**2000**	**6000**
Females				
Number of animals	30	30	30	30
Terminal body weight (g)	389.2±42.2	373.5±28.0	368.8±30.2* (-5.2)	347.7±30.6** (-10.7)
Uterus: non-gravid (g) 	0.62±0.19 0.16±0.05	0.60±0.17 0.16±0.05	0.58±0.16 0.16±0.04	0.52±0.23 (-16.1) 0.15±0.07
Ovary (g) (right) 	0.061±0.014 0.016±0.005	0.056±0.015 0.015±0.005	0.055±0.012 0.015±0.005	0.047±0.011** (-23.0) 0.014±0.005
Ovary (g) (left) 	0.061±0.013 0.016±0.005	0.058±0.016 0.015±0.005	0.054±0.013 0.015±0.005	0.049±0.014** (-19.7) 0.013±0.005
Brain (g) 	2.03±0.10 0.53±0.05	2.06±0.12 0.55±0.05* (3.8)	2.02±0.09 0.55±0.05	1.99±0.09 0.58±0.06** (9.4)
Liver (g) 	17.46±2.73 4.52±0.70	17.48±2.59 4.69±0.64	18.96±3.44 5.08±0.70** (12.4)	20.30±3.76** (16.3) 5.80±0.82** (28.3)
Spleen (g) 	0.76±0.12 0.20±0.04	0.70±0.11 0.19±0.02	0.68±0.11 0.18±0.03	0.73±0.13 0.21±0.04

[a] Data obtained from pages 321-322 and 380-381 in the study report (MRID 49192901).

[b] Numbers in parentheses are percent different from the control group, calculated by the Reviewer.

[c] Top row: absolute weight (g), bottom row, relative (to body) weight (g/kg bw)

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

b. Pathology:

1. **Macroscopic examination:** Overall, no treatment related gross lesions were observed in male or females rats of either generation. Observed lesions were considered unrelated to treatment because: 1) the incidences were not dose-dependent; 2) the lesions occurred in only one rat within a group; and/or 3) the observation was associated with other events unrelated to the test substance.

   F_0 generation: Gross lesions occurred in two male rats, one each in the 200 and 6000 ppm groups, and two female rats, one each in the control and 2000 ppm groups. In males, one 200 ppm group rat (10735) had small epididymides and purple and small testes. One 6000 ppm group rat (10818) had a white hard mass on the thymus, five dark red areas in the stomach, and hard and dark red apical and cardiac lobes of the lungs, considered related to a malignant thymoma, a spontaneously occurring tumor in this rat strain. Kidney lesions were present in the two females; the control group rat (10833) had moderately dilated pelvis, and the 2000 ppm group rat (10906) had yellow areas.

   F_1 generation: In males, observations were noted in 1, 2, 1, and 0 rats in the control, 200, 2000, and 6000 ppm groups, respectively. The control group rat (14825) and one 200 ppm rat (14857) had slight to moderate dilatation of the right renal pelvis; another 200 ppm group rat (14847) had a pale area on the spleen; and a 2000 ppm group rat (14876) had small epididymides and small purple and flaccid testes. In females, necropsy observations were noted in 2, 2, 1, and 0 rats in the same respective groups. These included a control group rat (15470) with a mass on the liver, a control

group rat (15479) with moderate dilation of the pelvis of the left kidney, a 200 ppm group rat (15486) with a dead fetus surrounded by a brown fluid in the right uterine horn (this dam did not deliver a litter), and a 200 ppm group rat (15483) and a 2000 ppm group rat (15539) with a mass in the left axilla.

2. **Microscopic examination:** As summarized in Table 8, histopathologic evaluation of tissues from F_0 and F_1 male and female rats revealed an increased severity of hemosiderosis in the spleen of the 6000 ppm group; this also was noted in F_0 females of the 2000 ppm group. This change consisted of an increased incidence of rats with a more severe degree of hemosiderin (hemosiderosis) in the splenic red pulp, with greater severity noted in the F_0 rats compared to the F_1 rats. There were no treatment-related effects in the spleen of the 200 or 2000 ppm males or 200 ppm females. There were no treatment related effects in the male or female reproductive organs in any group.

TABLE 8. Spleen histopathology observations- F_0 and F_1 animals [a]

Observation	Dietary concentration (ppm)							
	0	200	2000	6000	0	200	2000	6000
	Males				Females			
F_0 generation								
Number evaluated	30	29	28	30	30	30	30	30
Spleen- hemosiderosis								
Minimal	11	14	13	0	5	3	2	0
Slight	18	13	12	5	16	17	11	0
Moderate	1	2	3	18	8	9	13	14
Marked	0	0	0	7	1	1	4	16
Average severity [b]	1.67	1.59	1.64	3.07	2.17	2.27	2.63	3.53
F_1 generation								
Number evaluated	30	30	30	29	30	30	30	30
Spleen- hemosiderosis								
Minimal	28	30	27	8	20	17	13	6
Slight	2	0	3	17	8	11	15	18
Moderate	0	0	0	4	2	2	2	6
Average severity [b]	1.07	1.00	1.10	1.86	1.40	1.50	1.63	2.00

[a] Data taken from page 603-604 in the study report (MRID 49192901).

[b] Average severity was calculated by the Reviewer using the following point scale: minimal= 1; slight= 2, moderate=3, and marked= 4. ,..

B. OFFSPRING:

1. **Viability and clinical signs:** Mean litter size and viability (survival) results from F_1 and F_2 generation pups during lactation are summarized in Table 9. In both F_1 and F_2 pups, averages for number of implantation sites, liveborn pups, pups dying, delivered litter sizes, sex ratios, and Live Birth and Lactation Indices were unaffected by concentrations of the test substance as high as 6000 ppm. In F_1 pups in the 2000 ppm group, 14 (3.8%) pups died on PND 1 and eight (2.3%) pups died on PNDs 2 to 4, resulting in significantly reduced Viability Index. These differences were considered unrelated to the test substance because the incidences were not dose-dependent.

TABLE 9. Litter parameters for F_1 and F_2 generations [a]

Observation	Dietary concentration (ppm)			
	Control	200	2000	6000
F_1 Generation				
Number of litters	25	23	26 [b]	21
Number born live	344	284	363	309
Mean/dam	13.8±3.8	12.3±4.5	14.0±3.6	14.7±2.6
Number born dead	4	2	11	5
Mean/dam	0.2±0.5	0.1±0.3	0.4±1.2	0.2±0.7
Sex ratio day 1 (% %)	48.9±15.2	53.5±17.3	50.6±12.0	50.7±15.1
# Deaths days 1-4 (%) [c]	6 (1.7%)	2 (0.7%)	22 (6.1%) [d]	6 (1.9%)
# Deaths days 4-21 (%)	0	0	1 (0.5%)	0
Mean litter size Day 1	13.6±3.8	12.3±4.6	13.5±4.3	14.5±2.6
Day 4 [e]	13.5±3.7	12.3±4.5	13.6±3.5	14.4±2.5
Day 4 [f]	7.8±0.6	7.4±1.3	7.8±0.9	8.0±0.0
Day 7	7.8±0.6	7.4±1.3	7.7±0.9	8.0±0.0
Day 14	7.8±0.6	7.4±1.3	7.7±0.9	8.0±0.0
Day 21	7.8±0.6	7.4±1.3	7.7±0.9	8.0±0.0
Live Birth index (%)	98.3	97.9	96.3	98.4
Viability index (%)	98.2	99.3	93.9**	98.0
Lactation index (%)	100.0	100.0	99.5	100.0
F_2 Generation				
Number of litters	23	22	22	25
Number born live	357	315	315	378
Mean/dam	15.5±2.0	14.3±4.0	14.3±3.3	15.1±2.3
Number born dead	4	2	5	1
Mean/dam	0.2±0.8	0.1±0.3	0.2±0.7	0.0±0.2
Sex ratio day 1 (% %)	51.2±13.2	44.5±14.4	47.7±14.0	47.4±13.0
# Deaths days 1-4 (%) [c]	2 (0.6%)	7 (2.2%)	4 (1.3%)	5 (1.3%)
# Deaths days 4-21 (%)	2 (1.1%)	0	0	0
Mean litter size Day 1	15.5±2.1	14.3±4.0	14.3±3.3	15.1±2.3
Day 4 [e]	15.4±2.1	13.9±3.8	14.1±3.4	14.9±2.1
Day 4 [f]	8.0±0.0	7.6±0.8	8.0±0.0	8.0±0.2
Day 7	8.0±0.0	7.8±0.8	8.0±0.0	8.0±0.2
Day 14	7.9±0.3	7.8±0.8	8.0±0.0	8.0±0.2
Day 21	7.9±0.3	7.8±0.8	8.0±0.0	8.0±0.2
Live birth index (%) [c]	98.9	99.1	98.1	99.7
Viability index (%)	99.4	97.8	98.7	98.7
Lactation index (%)	98.9	100.0	100.0	100.0

[a] Data obtained from pages 199-202 and 396-399 in the study report (MRID 49192901).

[b] One litter had no surviving pups after day 1 postpartum, so n=25.

[c] Calculated by Reviewer from Day 1 and Days 2-4 data, not subject to statistical analysis.

[d] Number of deaths in the 2000 ppm group on both Day 1 and Days 2-4 were statistically different from control ($p<0.01$).

[e] Before standardization (culling)

[f] After standardization (culling)

** Statistically different from control, $p<0.01$.

No F_1 generation female pups died before scheduled sacrifice. Three 6000 ppm group male pups (2592, 14915, 14916) failed to thrive following weaning and were found dead on pre-mating days 2, 5 and 4, respectively. These pups were small for weaning age (≤ 42 grams). Evidence of dehydration in these pups included pale mucus membranes or red fluid in the bladder. No other deaths related to the test substance occurred.

There were no clinical observations caused by exposure to S-41311 at concentrations as high as 6000 ppm in either F_1 or F_2 male or female pups. Common clinical observations were noted and not related to treatment, including: cold to touch, pale, not nursing, and tip of tail missing or constricted. Observations noted at necropsy of the F_1 or F_2 pups were incidental and not considered treatment related.

2. **Body weight:** Selected mean pup body weight data are presented in Table 10. Body weight data for males and females, separately, were not reported, but were calculated by the reviewer from individual litter data (no statistical assessment). During the lactation period, the F_1 and F_2 pups in the 6000 ppm group had significantly decreased mean body weights (-9% to -21% and -7% to -21%, respectively), with the magnitude of the deficits increasing with time. Significantly reduced body weights were noted on PNDs 1 to 21 in F_1 pups and on PNDs 4 (pre- and post-culling) to 21 in the F_2 pups. The magnitude of the deficit in body weight of the F_1 male pups (9%) and F_1 female pups (8%) on lactation day (LD) 1 was similar to the deficit observed in the F_2 male pups (8%) and F_2 female pups (7%) on LD 4.

TABLE 10. Mean (±SD) Litter and pup weights (g) [a]

Lactation Day or interval	Dietary concentration (ppm) 0	200	2000	6000	0	200	2000	6000
	F_1 Litters- absolute body weight				F_2 Litters- absolute body weight			
LD 1	6.7±0.8	6.8±0.5	6.6±0.6	6.1±0.8** (-9) [b]	6.2±0.4	6.4±0.6	6.4±0.5	6.0±0.4
LD 4 [c]	10.0±1.7	10.2±1.5	9.5±1.5	8.4±1.2** (-16)	8.8±1.0	9.5±1.6	9.3±1.2	8.2±0.8** (-7)
LD 4 [d]	10.0±1.7	10.2±1.5	9.5±1.5	8.4±1.2** (-16)	8.9±1.0	9.6±1.5	9.4±1.1	8.2±0.8** (-8)
LD 7	16.8±2.3	16.6±2.0	16.1±2.0	13.8±1.8** (-18)	15.3±1.8	16.2±2.0	15.6±1.7	13.8±1.2** (-10)
LD 14	35.4±4.0	35.0±3.0	35.0±3.0	29.1±2.6** (-18)	33.5±2.2	34.7±3.5	33.4±2.5	28.5±2.8** (-15)
LD 21	55.5±5.7	55.6±4.3	53.1±4.8	44.0±2.5** (-21)	52.3±3.7	54.9±5.3*	50.3±3.7	41.6±3.8** (-21)
	F_1 Litters- body weight gains [e]				F_2 Litters- body weight gains [e]			
LD 1-4 [c]	3.3±1.0	3.4±1.1	2.9±1.0	2.3±0.7	2.6±0.8	3.1±1.1	2.9±0.8	2.2±0.5
LD 4 [d]-14	25.4±3.0	24.8±2.2	25.5±2.3	20.6±1.9	24.6±1.7	25.1±2.5	24.0±2.0	20.2±2.3
LD 14-21	20.1±2.6	20.6±2.4	18.1±2.3	15.0±1.4	18.8±2.3	20.2±2.4	16.9±1.9	13.1±1.8
LD 1-21	48.8±5.2	48.8±4.0	46.5±4.5	37.9±2.1	46.1±3.6	48.5±4.8	43.9±3.4	35.7±3.6
	F_1 Male Pups– absolute body weight [e]				F_2 Male Pups – absolute body weight [e]			
LD 1	6.9±0.8	6.9±0.5	6.8±0.7	6.3±0.7 (-9)	6.4±0.4	6.6±0.6	6.6±0.6	6.1±0.4 (-4)
LD 4 [c]	10.2±1.7	10.3±1.5	9.8±1.5	8.6±1.2 (-15)	9.1±1.1	9.7±1.6	9.6±1.2	8.4±0.9 (-8)
LD 4 [d]	10.3±1.7	10.4±1.5	9.8±1.5	8.6±1.2 (-16)	9.2±1.0	9.8±1.6	9.6±1.2	8.5±0.9 (-8)
LD 7	17.2±2.3	16.9±2.0	16.4±2.0	14.1±1.8 (-18)	15.7±1.9	16.4±2.1	16.1±1.9	14.1±1.3 (-10)
LD 14	35.8±4.1	35.5±2.9	35.5±3.1	29.6±2.7 (-17)	34.2±2.2	35.1±3.8	34.1±2.7	29.0±3.0 (-15)
LD 21	56.3±5.9	56.3±4.5	54.0±5.1	45.0±2.8 (-20)	53.0±3.8	55.4±5.6	51.4±4.0	42.4±4.1 (-20)
	F_1 Male Pups– body weight gains				F_2 Male Pups– body weight gains			
LD 1-4 [c]	3.3±1.0	3.4±1.1	3.0±1.0	2.4±0.7	2.7±0.8	3.1±1.2	3.0±0.8	2.3±0.5
LD 4 [d]-14	25.6±3.1	25.1±2.3	25.7±2.3	21.0±1.9	25.0±1.7	25.3±2.7	24.5±2.1	20.5±2.5
LD 14-21	20.5±2.7	20.8±2.7	18.5±2.4	15.4±1.4	18.9±2.4	20.4±2.4	17.3±2.1	13.4±1.9
LD 1-21	49.4±5.4	49.4±4.3	47.2±4.8	38.7±2.3	46.7±3.7	48.9±5.1	44.8±3.7	36.2±3.8
	F_1 Female Pups– absolute body weight [e]				F_2 Female Pups– absolute body weight [e]			
LD 1	6.5±0.8	6.6±0.5	6.5±0.7	6.0±0.8 (-8)	6.0±0.4	6.3±0.7	6.2±0.6	5.8±0.4 (-3)
LD 4 [c]	9.8±1.7	9.9±1.3	9.3±1.6	8.3±1.2(-16)	8.6±0.9	9.3±1.6	9.0±1.2	8.0±0.9 (-7)
LD 4 [d]	9.8±1.7	9.9±1.3	9.4±1.5	8.2±1.1 (-16)	8.7±1.0	9.5±1.6	9.1±1.2	8.1±0.9 (-7)
LD 7	16.4±2.3	16.0±1.7	15.9±2.1	13.7±1.9 (-17)	15.0±1.8	16.0±2.1	15.2±1.7	13.5±1.2 (-10)
LD 14	35.0±4.0	34.2±2.8	34.6±3.2	28.6±2.7 (-18)	32.9±2.3	34.3±3.3	32.7±2.5	28.0±2.7 (-15)
LD 21	54.7±5.6	54.4±4.0	52.3±4.5	43.2±2.4 (-21)	51.6±3.7	54.4±5.2	49.2±3.6 (-5)	40.9±3.8 (-21)
	F_1 Female Pups– body weight gains				F_2 Female Pups– body weight gains			
LD 1-4 [c]	3.3±1.0	3.3±0.9	2.9±1.1	2.3±0.7	2.6±0.8	3.1±1.1	2.8±0.9	2.2±0.6
LD 4 [d]-14	25.2±2.9	24.4±2.1	25.3±2.4	20.3±2.0	24.2±1.7	24.9±2.3	23.6±2.0	20.0±2.3
LD 14-21	19.7±2.6	20.2±2.3	17.6±2.3	14.6±1.4	18.7±2.2	20.0±2.5	16.5±2.0	12.8±1.9
LD 1-21	48.2±5.2	47.8±3.7	45.8±4.2	37.2±2.0	45.6±3.6	48.1±4.7	43.1±3.3	35.1±3.5

[a] Data obtained from pages 202, 276-279 and 399, 468-471 in the study report (MRID 49192901).

[b] Values in parentheses represent percent difference from control, calculated by Reviewer.

[c] Before standardization (culling)

[d] After standardization (culling)

[e] Weight gains and male and female body weights were calculated by Reviewer from individual litter data (pages 272-275 and 468-471); not subject to statistical analysis.

* Statistically different from control, $p<0.05$.

** Statistically different from control, $p<0.01$.

3. Sexual maturation: Parameters of sexual maturation, such as anogenital distances, were not measured.

4. Offspring postmortem results:

a. Organ weights: Organ weights were not evaluated for weanling animals.

b. Pathology: Pathology was not assessed in weanling animals, unless they died before scheduled sacrifice. No treatment related effects were noted for these animals.

c. Skeletal evaluations: Skeletal evaluations were conducted for F_2 pups only and are summarized in Table 11. Pups culled on PNDs 4 or 21 had no anomalies. Significant increases in the number of pups (and litters) with unilateral or bilateral 14th ribs (variants) occurred in the 2000 and 6000 ppm groups on PND 4 and in the 6000 ppm group on PND 21. Also in the 6000 ppm group, the pup (and litter) incidences of bifid thoracic centrum were significantly increased on PND 4. Statistically, the average number of ossification sites differed in ribs and vertebrae (lumbar and thoracic) of rats in the 2000 and 6000 ppm groups, but the differences were small (<5%) and within the range of presented historical control data and therefore, not considered biologically significant. Fetal and litter incidences of delayed or unossified sites were not included in the study report.

TABLE 11. Skeletal examinations- F_2 generation [a]

Observations [b]	Dietary concentration (ppm)			
	0	200	2000	6000
PND 4: Variants				
#Pups (litters) examined	171 (23)	137 (20)	135 (21)	175 (24)
Vertebrae- bifid thoracic centrum [b]	0	0	0	5** (5)**
Ribs- unilateral or bilateral, 14th	46 (15)	31 (11)	65** (19)*	88** (22)**
% of fetuses	26%	22%	48%	50%
% of litters	65%	55%	90%	92%
PND 4: Ossification sites				
#Pups(litters) examined	178 (23)	143 (20)	145 (21)	177 (24)
Vertebrae- lumbar [c]	5.72±0.30	5.79±0.27	5.45±0.32** (-4.7) [d]	5.52±0.29* (-3.5)
- thoracic	13.28±0.30	13.20±0.27	13.54±0.31** (2)	13.47±0.27
Ribs (pairs)	13.21±0.24	13.15±0.23	13.41±0.27* (1.5)	13.75±1.67* (4.1)
PND 21: Variants				
#Pups (litters) examined	182 (23)	170 (22)	176 (22)	198 (25)
Ribs- unilateral or bilateral, 14th	1 (1)	1 (1)	4 (2)	27** (12)**
PND 21: Ossification sites				
#Fetuses(litters) examined	182 (23)	170 (22)	176 (22)	198 (25)
Vertebrae- lumbar [c]	6.00±0.02	5.99±0.05	5.98±0.09	5.87±0.19** (-2.2)
- thoracic	13.00±0.02	13.00±0.02	13.02±0.09	13.13±0.21** (1)
Ribs (pairs)	13.00±0.02	13.00±0.02	13.02±0.07	13.12±0.20** (1)

[a] Data obtained from pages 402-405, MRID 49192901.

[b] Pup (litter) incidence

[c] Ossification sites/pup/litter, Mean ± S.D.

[d] Numbers in parentheses are percent different from the control group, calculated by the Reviewer.

* Statistically different ($p < 0.05$) from the control.

** Statistically different ($p < 0.01$) from the control.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: Based on the results of this study, **the no-observable-adverse-effect-level (NOAEL) for S-41311 in F_0 generation adult male rats was 2000 ppm and in female rats was 200 ppm.** Reduced body weight and feed consumption values and increased liver weights occurred in the 6000 ppm group males and females. Histopathologic evaluation of tissues from the F_0 generation rats revealed an increased severity of hemosiderosis in the spleen of the 6000 ppm group males and the 2000 and 6000 ppm group females.

The NOAEL for S-41311 in F_1 generation adult male and female rats was 200 ppm. Reduced body weight and feed consumption values occurred in the 2000 ppm group males and females. Histopathologic evaluation of tissues from both the male and female rats revealed an increased severity of hemosiderosis in the spleen of the 6000 ppm group rats.

The NOAEL for S-41311 for male and female reproductive performance for both generations was 6000 ppm. Exposure to concentrations as high as 6000 ppm did not affect mating performance or fertility of the male and female rats. There were no treatment-related effects in the male or female reproductive organs in any group.

The NOAEL for S-41311 was 2000 ppm in the F_1 pups and 200 ppm in the F_2 pups. The 6000 ppm concentration reduced pup body weights in both generations. In the F_2 pups, an increase in rib pairs and 14th ribs occurred in the 2000 ppm (day 4) and 6000 ppm (day 4 and day 21) groups (only the F_2 generation was evaluated for skeletal alterations).

B. REVIEWER COMMENTS: In general, the Reviewer agrees with the conclusions of the study authors. The main effects observed in parental F_0 and F_1 animals were reduced body weight gain and/or body weight along with decreased food consumption during the pre-mating period, noted primarily in the 6000 ppm group, with some smaller and less persistent effects in the 2000 ppm group. In general, effects on body weight gains and food consumption were more pronounced in males compared to females in the F_0 generation, and tended to even out in the F_1 generation. The decreases in absolute body weights were more pronounced in the F_1 generation compared to the F_0 generation rats, with significant reductions noted throughout the pre-mating period for F_1 males and females and F_0 males of the 6000 ppm group and during portions of the pre-mating period for F_1 rats in the 2000 ppm group. Likewise, reductions in food consumption were more dramatic in the F_1 generation versus the F_0 generation, with decreases noted in F_0 rats in the 6000 ppm group and in F_1 rats in both the 2000 and 6000 ppm groups. After mating, average body weight gains were significantly reduced in the 2000 and 6000 ppm group F_0 male rats, but the difference at 2000 ppm was similar to the difference seen in the 200 ppm group, and therefore unlikely to be of biological significance during this time period. During the gestation and lactation periods, the F_1 generation dams were again more sensitive to significant differences in body

weight and food consumption compared to F_0 dams, with reductions observed in F_1 dams of the 6000 ppm group while F_0 dams were comparable across all groups. Terminal body weights were decreased in F_0 rats of the 6000 ppm and in F_1 rats of both the 2000 (females only) and 6000 ppm groups. Increases in liver weights for rats of both generations (F_1 females only) and reductions in brain (male) and ovarian (female) weights for F_1 rats in the 6000 ppm group were not accompanied by histopathological effects, therefore the biological significance of these effects are uncertain. The F_0 rats appeared more sensitive to an increased severity of hemosiderosis in the spleen, with differences noted in F_1 rats at 6000 ppm and in F_0 rats at 2000 ppm (females only) and 6000 ppm (both sexes).

The parental systemic LOAEL for imiprothrin in rats was 2000 ppm (125.5 and 143.5 mg/kg bw/day in F_0 males and females; and 157.7 and 175.1 mg/kg bw/day in F_1 males and females, respectively), based on reduced body weight and food consumption in males and females of the F_1 generation and an increased severity of hemosiderosis in the spleen of F_0 generation females. The parental systemic NOAEL is 200 ppm (12.4 and 14.7 mg/kg bw/day in F_0 males and females; and 15.6 and 17.5 mg/kg bw/day in F_1 males and females, respectively).

Significant effects on offspring parameters included decreased body weights in the F_1 and F_2 pups in the 6000 ppm group during the lactation period and increased incidence of the skeletal variants unilateral and bilateral 14^{th} ribs in the 2000 ppm and 6000 ppm F_2 pups (and litters). Significant differences observed in ossification sites were small, and within or just outside the range of historical control values, and therefore were not considered adverse.

The offspring LOAEL for imiprothrin in rat pups was 2000 ppm (126 and 144 mg/kg bw/day in males and females, respectively), based on increased incidence of rib variants (unilateral or bilateral 14^{th} ribs) in F_2 generation pups. The offspring NOAEL is 200 ppm (12.4and 14.7 mg/kg bw/day in males and females, respectively). At 6000 ppm (369 and 423 mg/kg/day in F_0 males and females), decreased offspring (F_1 and F_2) body weights and an increase in the incidence of unilateral or bilateral 14^{th} ribs in PND 21 F_2 offspring were observed.

There were no treatment related effects on mating performance, fertility, or reproductive organs in the male or female rats of the F_0 or F_1 generation at dietary levels as high as 6000 ppm, with the exception of reduced ovarian weights in the F_1 females. Without accompanying changes in histopathology or function effects on mating performance or fertility, the biological significance of this increase is uncertain. **Therefore, the reproductive toxicity LOAEL was not identified; the reproductive toxicity NOAEL for imiprothrin in rats was 6000 ppm (369 and 423 mg/kg bw/day in males and females, respectively).**

C. STUDY DEFICIENCIES:

Sperm were not evaluated for parameters such as count, morphology, and motility. Further, although estrous cycling was monitored during the mating period, guidelines require evaluation for at least 3 weeks prior to mating and throughout the mating period. Landmarks of sexual maturation, including the age of vaginal opening, preputial separation, and

anogenital distance, were not measured in pups. Kidney and adrenal glands were not weighed, and no organs were weighed in the F_2 pups (brain, spleen and thymus recommended for 1 pup/sex/litter). These are requirements of the 1998 Health Effects Test Guidelines for Reproductive Toxicity and Fertility (OPPTS 870.3800) and were not requirements at the time of the study (1994).

Further, post-implantation loss and F_1 and F_2 litter body weight gains and male and female litter body weights were not included in the report but were calculated by the Reviewer from data provided. Fetal and litter incidences of delayed or unossified sites were not included in the study report.

APPENDIX: Reproductive Toxicity: Dose Range-Finding Study in Rats (Argus Research Laboratories, Inc., Protocol 1119-024P)

TEST MATERIAL (PURITY): S-41311 (Imiprothrin, 100% a.i.)

Methodology for this range-finding study was not included in the main study report. From the reported results, dose selection in male and female rats included dietary concentrations of S-41311 at 3000, 6000, and 10,000 ppm. Range-finding results are as follows:

Parental Parameters: No test substance-related deaths, clinical observations, or necropsy observations occurred in the F_0 generation male or female rats at concentrations of S-41311 as high as 10,000 ppm.

In males, body weight, body weight gains, and food consumption values tended to be reduced or were significantly reduced in the 3000, 6000 and 10,000 ppm group rats during the pre-mating period, although the magnitude of the deficits was not provided. It was stated that the deficits in these groups probably reflect taste aversion, which was noted during the first week of treatment. Terminal body weights tended to be reduced in the 3000 and 6000 ppm groups and were significantly reduced in the 10,000 ppm group males. During the first month of the pre-mating period, female body weight gains tended to be reduced or were significantly reduced in the 3000, 6000 and 10,000 ppm groups, with average food consumption values also significantly reduced in the 6000 and 10,000 ppm group rats, likely associated with the taste aversion that occurred in the first week of the study. During gestation and lactation, maternal body weights, body weight gains, and food consumption values tended to be reduced or were significantly reduced in the 6000 and 10,000 ppm groups (magnitude of deficits not reported). Reductions in the 10000 ppm group females persisted, while the differences in the 6000 ppm group were small and transient. Terminal body weight data for females were not described.

Reproductive Parameters: Concentrations of S-41311 as high as 10,000 ppm did not affect the mating performance or fertility of the male or female rats, and did not affect absolute weights of the male reproductive organs (no information was provided for female reproductive organs).

Offspring Parameters: Significant reductions in pup body weights (data not provided) occurred in the 6000 and 10,000 ppm groups during the postpartum period. Delivery parameters (duration of gestation, implantations, stillborn pups, surviving pups per litter, live litter size at weighing and sex ratios), clinical observations, and necropsy observations were unaffected by concentrations of S-41311 as high as 10,000 ppm.

Based on the results of the dose-range finding study, concentrations of imiprothrin in the diet for the two-generation reproductive toxicity study were set at 0, 200, 2000, and 6000 ppm.

The lack of any quantification of the body weight effects makes it difficult to assess whether the 10000 ppm dose level should have been selected as the high dose for the definitive study.